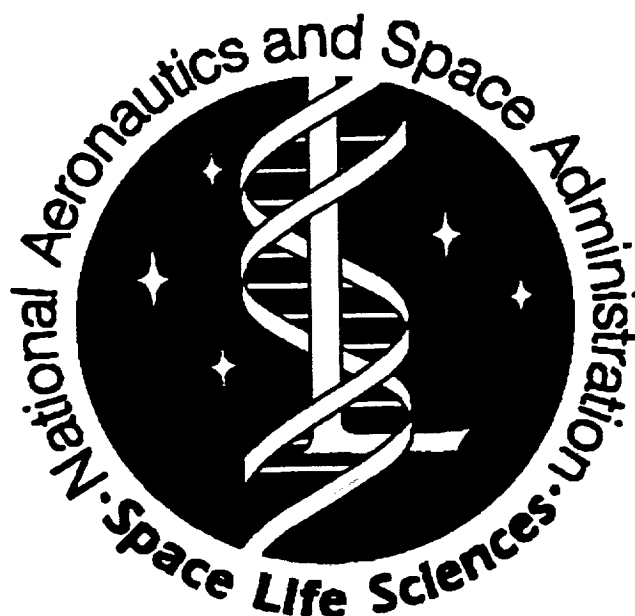


MUSCULOSKELETAL DISCIPLINE SCIENCE PLAN

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**SPACE PHYSIOLOGY AND COUNTERMEASURES PROGRAM
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MUSCULOSKELETAL DISCIPLINE SCIENCE PLAN

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MUSCULOSKELETAL DISCIPLINE SCIENCE PLAN

1.0 INTRODUCTION

As the U.S. Space Program prepares for extended-duration space flights on the Space Shuttle, on Space Station Freedom, and on exploration missions to the Moon and Mars, life sciences research must provide an understanding of the physiological changes that occur and develop effective countermeasures to any effects that may be detrimental to the functional capacity, health, or well-being of crewmembers. Weightlessness is a unique environment; therefore, it is important to investigate the effects of this newly inhabited environment on human physiology. Life sciences research in this discipline must identify possible consequences of weightlessness on the musculoskeletal system, understand the mechanisms of these effects, and develop effective and operationally practical countermeasures to protect crewmembers.

The musculoskeletal system is highly plastic in that it possesses the inherent capability to adapt its structural and functional properties in accordance with the type and degree of stimuli imposed on it. Prolonged space travel is essentially a period of significant unloading of the musculoskeletal system. This results in adaptive responses in the structure and function of this system, placing it on the low end of a continuum from one of complete disuse to one of maximal use. There is a high probability that the musculoskeletal system is functionally impaired with increasing duration of weightlessness.

1.1 PURPOSE

The purpose of this Discipline Science Plan is to provide a conceptual strategy for NASA's Life Sciences Division research and development activities in the area of musculoskeletal function. This document summarizes the current status of the program, outlines available knowledge, establishes goals and objectives, identifies science priorities, and defines research opportunities, which encompass critical questions in the subdiscipline areas (e.g. muscle, bone, and other musculoskeletal connective tissues). These science activities include ground-based and flight; basic, applied, and operational; and animal and human research and development. This document contains a general plan that will be used by both NASA Headquarters Program Offices and the field centers to review and plan basic, applied, and operational intramural and extramural research and development activities in this area.

1.2 BRIEF DESCRIPTION OF THE DISCIPLINE

The NASA Life Sciences Musculoskeletal Program is a multidisciplinary research field that encompasses basic, applied, and operational research to understand the effects of weightlessness on the musculoskeletal system, including cellular and subcellular mechanisms, so that the undesirable effects can be prevented or successfully reversed. Among the disciplines currently encompassed by this research are epidemiology; exercise physiology; neuromuscular and orthopedic biomechanics;

muscle and bone physiology studying perfusion, metabolism and substrate utilization, protein synthesis, and muscle anabolism and catabolism; developmental biology; histomorphology; cellular biology; biochemistry; stereochemistry; endocrinology; and molecular biology.

Ground-based studies involve both human and animal (rats and nonhuman primates) subjects. Many of these studies use analogs of weightlessness, including bedrest, horizontal or head down, water immersion, and immobilization and hind-limb suspension of rats. They involve the use of state-of-the-art equipment, including x-ray bone densitometers, magnetic resonance imaging and spectroscopy, gait analysis, isokinetic dynamometry, and computed tomography.

Flight research, which also uses both human and animal subjects, primarily addresses the questions of "What happens to the musculoskeletal system during weightlessness?" and "What effects do certain countermeasures have?" These flight data have been obtained from subjects on both U.S. and U.S.S.R. missions. Countermeasures that have been examined on the ground and/or in flight include various types and prescriptions of exercise, electrical stimulation, pharmacology, changes in nutrition, and muscle stretch. Artificial gravity is a potential countermeasure for musculoskeletal effects of space flight.

1.3 GOALS AND OBJECTIVES

1.3.1 Goals

The overall goals of the NASA Musculoskeletal Discipline Research Program are to:

- Understand the musculoskeletal system's adaptation to space flight
- Ensure adequate physiological and performance countermeasures

The achievement of these goals is predicated on specific objectives concerned with understanding the mechanisms whereby the organism, tissue, cells, organelles, and extracellular matrix of muscle, bone, and connective tissue

- achieve and maintain Earthbound homeostasis
- function in either a microgravity environment or under conditions of non-weightbearing
- undergo adaptive changes in structure and function in response to prolonged exposure to a microgravity environment
- respond to a variety of countermeasures (mechanical, hormonal, pharmacologic) designed to maintain normal structure and function in the face of prolonged exposure to a microgravity environment as well as undergo readaptation to Earth's gravity

1.3.2 Objectives

The specific objectives leading to the attainment of the goals of the research program are to:

- Determine the acute and long-term responses and consequences of the muscular and skeletal adaptation to microgravity
- Determine crew performance or mission consequences of muscular and skeletal responses to microgravity
- Understand the mechanisms of muscular and skeletal adaptations to microgravity, both acute and long-term
- Develop and verify muscular and skeletal countermeasures that will facilitate a rapid physiological transition from microgravity to gravity
- Develop and verify ground-based human and animal models to study musculoskeletal changes.
- Develop and verify biomechanical models to investigate neuromuscular and musculoskeletal mechanics during normal activities, including exercise, in microgravity, 1-g, and hypergravity environments.
- Develop and verify computer models of adaptation to study muscle, bone, and connective tissue at the tissue level.

This plan incorporates recommendations from reports by the Committee on Space Biology and Medicine (Goldberg), the NASA Life Sciences Strategic Planning Study Committee (Robbins), and the Federation of American Societies for Experimental Biology (FASEB) (see List of References).

Current knowledge about physiological changes associated with short-term and long-term space flight is summarized in Appendix I, which is from Space Physiology and Medicine, 2nd edition, by Drs. Nicogossian, Leach Huntoon, and Pool.

2.0 BONE, MINERAL, AND CONNECTIVE TISSUE

2.1 BACKGROUND AND CURRENT KNOWLEDGE

The following results have been noted in actual and simulated space flight:

- Connective tissue strength, stress, stiffness, and elastic modulus are decreased.
- Bone crystal size is decreased.
- Lipid inclusions in bone are increased.

- Angiogenesis in bone is reduced.
- Bone callus formation is decreased.
- Bone demineralization occurs, particularly in weight-bearing bones.
- Skin hyperplasia occurs.
- Matrix protein formation is reduced.
- Urinary excretion of calcium and collagen fragments is increased.
- The muscular extracellular space is expanded.
- Collagen concentration of atrophied muscle is increased.
- Tendon collagen is lost.
- Water content of intervertebral discs is reduced.
- Trabecular bone density is decreased.
- Production of precursor cells (osteoprogenitor cells) is reduced.
- Bone loss is proportional to duration and quantity of unloading.
- Urine concentration of stone-forming salts is increased.

Connective tissues are structural tissues that maintain the stability of joints and are involved in the translation of forces (muscular and external). Human and animal studies have reported significant changes in connective tissue structure and composition during actual space flight and ground-based simulations of space flight such as bedrest and hindlimb unloading.

Most of the NASA research effort in the connective tissue area has been focused towards bone physiology. Flight experiments on short- and long-duration (COSMOS, Mir, Spacelab and Skylab) missions have confirmed that weightlessness reduces the specific gravity (density) of bone. The microgravity-induced decrease in bone density includes a variety of factors such as increased bone resorption, reduced bone formation, and diminished mineralization. Also, bone quality is compromised by space-flight, leading to increases in porosity, reductions in bone crystal size, alterations in the crosslinking of collagen, changes in bone microstructure and geometry, and variations in the regional distribution of bone structural proteins. Flight-induced alterations in bone structure are believed to result from changes in bone metabolism. These changes could result in stress fractures in flight.

Human and animal data indicate that short- and long-duration weightlessness modifies the metabolism of bone. The use of bone markers for labeling new bone formation indicated that microgravity has a suppressive effect on bone formation. Also, metabolic markers of bone resorption, such as urinary excretion of hydroxyproline and calcium, increased in astronauts on Skylab. Ground-based animal and human models showed similar findings to flight studies and confirmed alterations in calcium metabolism. The high levels of calcium salts in body fluids of astronauts enhance the probability of forming insoluble salts such as kidney stones. Furthermore, cell culture experiments from flight animals also revealed that space-flight reduces the capacity to form bone precursor cells (osteoprogenitor cells), thus affecting the process of connective tissue cell differentiation. Preliminary information obtained from COSMOS Biosatellite animal studies showed that fracture healing is significantly impaired during weightlessness. In essence, the microgravity environment alters the steady-state condition of bone by causing perturbations in physiological processes associated with mineral metabolism, protein synthesis and organization, and cell differentiation. Light and electron microscopic studies of bone tissue obtained from space-flight (COSMOS Biosatellite) showed that endosteal osteoblasts and the periosteal vasculature were significantly changed. Signs of moderate degeneration were observed, such as accumulation of lipids and vascular disruption. The bone repair studies indicated a reduced angiogenesis, thus producing little or no callus (phase of repair) during flight.

Obviously, alteration in bone organization impacts on its mechanical properties. Bone tissue biomechanical studies have verified that microgravity modifies the structural and material properties of bone. Bones from flight rats were weaker, less stiff, lower elastic modulus and lesser flexural rigidity as compared to ground-based controls. Hindlimb unweighting studies revealed similar results.

Other connective tissue types are also affected by the microgravity environment. For example, the recent COSMOS 1887 studies on growth plate cartilage disclosed that the proliferative zone was enlarged, whereas the hypertrophic and resting zones were reduced. These findings suggested that chondrogenesis was suppressed by microgravity. Additional evidence supporting the hypothesis that space-flight has a suppressive effect on chondrogenesis can be confirmed from flight experiments that have documented shorter bones and slower growth. It is known that longitudinal bone growth is a function of chondrogenesis and osteogenesis. Therefore, the microgravity-induced shortness of the long bones may result from the suppressive effect upon chondrogenesis and osteogenesis. Also, preliminary analysis of vertebral discs obtained from flight animals on COSMOS 2044 showed that water content is reduced.

Hindlimb unweighting studies also showed that tendons had lower collagen and proteoglycan concentrations as compared to age-matched, weight-bearing rodents. Alterations were observed in the collagen and proteoglycan of patellar tendons of flight animals. Since collagen is highly correlated to tendon strength, a loss of this major protein (collagen constitutes 80 percent tendon dry weight) would result in a significant decrement in tendon maximum strength. Although ligaments have yet to be evaluated in flight animals, ground-based studies have documented that ligament junction strength is significantly decreased after 7-14 days of limb unweighting. Since ligaments insert into bones, it is possible that demineralization of bone during space-flight may weaken the insertions of ligaments. This would have an important bearing

on the risk of incurring ligamentous injury during space-flight, extravehicular activities, emergency egress, and recovery. Other findings involving soft connective tissue changes during space-flight included preliminary reports that showed increases in cell number and DNA content of the skin and greater collagen concentrations of atrophied soleus muscles.

It is known that connective tissues are responsive to mechanical stresses and hormones; however, at present, it is difficult to ascertain whether connective tissue alterations during exposure to microgravity are the result of changes in mechanical stresses and/or variations in circulating hormones.

2.2 CRITICAL QUESTIONS (In priority order)

2.2.1 Organ Physiology

1. What are the rate, extent, and time course of bone and connective tissue loss for different areas of the body during exposure to microgravity or simulated microgravity? How is the time course of regional tissue loss correlated with changes in the tissue stress and strain histories at the same site? To changes in regional microcirculation? To other regional and systemic factors?
2. Which endocrine and nutritional processes are required for maintenance of bone and connective tissue? How do these processes interact with mechanical loading? Are these processes affected by space-flight?
3. What are specific countermeasures that impact effectively upon bone and connective tissue structure and function?
4. What potential risks does bone loss present to the development of bone fractures, hypercalcemia, metastatic calcification, and renal stone formation?
5. What are the similarities and differences of ground-based models and space flight-induced bone and connective tissue loss with respect to biomechanical, histomorphometric, biochemical, and hormonal changes?
6. Is bone loss reversible in terms of mass, ultra- and micro-structural organization, and microstructure? To what extent do irreversible architectural adaptations affect structural integrity?
7. What are accurate histomorphological and architectural descriptions of the changes that occur in bone and connective tissue because of space-flight?
8. How do mechanical stress and changes in stress contribute to bone and connective tissue formation? Are stress and/or changes in stress required for continued structural integrity?

9. What are the critical characteristics or components of normal daily tissue stress and strain histories that regulate bone and connective tissue development, maintenance, and adaptation? How are these characteristics affected by microgravity?
10. How are regional changes in bone and connective tissue related to regional changes in muscle tissue?
11. How are neuromuscular activation patterns and musculoskeletal mechanics altered during activity (including exercise) in microgravity compared to 1-g.

2.2.2 Cellular and Molecular

1. How are the patterns of normal organismic in-vivo mechanical loading (e.g., tissue strain, stress, strain rate, stress rate) best characterized and quantified (e.g., peak strains, peak stresses, energy content)?
2. Formulate mathematical and computer models of tissue adaptation and cellular transient response to altered load histories.
3. What are the bone and connective tissue markers of metabolism (protein synthesis, secretion, and degradation)? How can bone marker data be used to investigate and predict regional changes in bone metabolism?
4. Which endocrine-receptor perturbations modulate tissue responsiveness to mechanical stresses?
5. Which specific models predict bone and connective tissue structural transients during altered load environments?
6. What key elements of bone and connective tissue structural assembly impact the biomechanical properties?
7. Are there specific load histories that affect the macromolecular assembly of connective tissues?
8. What are specific signal transduction processes relevant to the modulation of structural molecules during altered load histories?
9. How do changes in mechanical forces and tissue stress (e.g., shear, stress) and/or electrical forces (piezoelectric and tissue streaming potentials) result in mechanisms that are associated with translational alterations in connective tissue structural proteins?
10. Is cytokine production and response to cytokines by osteoblasts and osteoclasts affected by exposure to microgravity?

11. Are precursor cells of osteoblasts and osteoclasts affected by microgravity?
12. Do precursor bone cells respond to maturation stimuli in a microgravity environment as they do on earth?
13. Do osteoblasts require gravity to function normally? If bone development was to occur in a microgravity environment so that bone cells never saw gravity would they function normally throughout the life-span of the animal?

3.0 MUSCLE

3.1 BACKGROUND AND CURRENT KNOWLEDGE

Previous studies (both ground-based and flight involving animals and humans) have provided information to suggest space-flight-induced alterations in muscle structure and function. Some of the most profound changes in muscles are as follows

Human Skeletal Muscle

- Prolonged joint immobilization results in major reductions in the fiber area of both type I and type II fibers.
- Following bedrest there are losses in fiber areas of both major fiber types in muscle.
- Ultrastructural evidence of muscle fiber damage occurs in human skeletal muscle after bedrest.
- Decrements in muscle strength and endurance occur following both space-flight and bedrest.
- Exercise programs appear to retard losses in muscle structure and function during bedrest and space flight.
- The relationship between EMG and force is altered following space-flight.
- Crewmembers report extreme and short-term muscular weakness following space-flight.
- In bedrest, strength loss is related to loss of muscle mass in the lower limbs.
- Endurance-type exercise during space flight appears to retard but not eliminate losses in size and function of muscle.

- Electrical stimulation during bedrest can retard losses of muscle structure and function.

Animal Skeletal Muscle

- Antigravity muscles, comprised chiefly of slow-twitch fibers, undergo greater degrees of atrophy than their respective fast-twitch synergists.
- Fiber atrophy involves changes in cross-sectional area and the preferential losses of contractile protein as compared to other protein pools within the fiber.
- Slow-myosin isoforms are decreased and fast-myosin isoforms are increased in antigravity muscles during space flight and in hindlimb-suspended rats, thereby altering the contractile properties of the muscle.
- The responses in muscles of hindlimb-suspended rats and those flown in space are similar, demonstrating that this model is useful for studying the mechanisms of muscle atrophy.
- As a consequence of unloading, protein synthesis and protein degradation processes are altered, with the former being depressed and the latter accelerated in the transition to a new steady state of reduced muscle mass.
- Changes in protein expression during atrophy involve alterations in both transcriptional and translational processes.
- Skeletal muscle repair is delayed during space-flight.
- Antigravity muscles have the capacity to regain normal mass and protein isoforms upon recovery from non-weight-bearing states.
- Hormonal interventions such as growth hormone and anabolic steroids may reduce the atrophic response in response to unloading.
- Thyroid hormone plays a regulatory role in myosin isoform switching in response to unloading.
- There is a differential response between the loss of mitochondrial and myofibrillar proteins following space-flight.
- Conventional activity paradigms such as endurance training and intermittent weight-bearing are only partially effective in preventing the atrophy associated with unloading.

Early reports on man in space have provided several lines of indirect, but compelling, evidence that skeletal muscle atrophies in the microgravity environment. Decreases in leg girth and muscle strength of crew members have been reported. Consistent with

these findings were metabolic studies that showed negative protein and phosphorous balances. Further suggestion of atrophy has come from studies that revealed an increase in ratio of muscle electrical activity (EMG) to work performed and an increased fatigability. Recent studies of muscle biopsies taken from astronauts before and after flight have provided some evidence of muscle atrophy during space flights of 5 to 11 days. Type I and type II fibers both sustained significant decreases in cross-sectional area during space flight. The type I fibers also showed increased expression of the fast myosin isoform; but exposure to microgravity did not affect abundance of two key metabolic enzymes, succinic dehydrogenase and alphaglycerophosphate dehydrogenase. This provides strong evidence that the human muscle atrophies during space travel. There is suggestion that endurance-type exercise by astronauts will retard, but not prevent, loss of muscle function and mass.

Earth-based studies on human beings, using bed rest or joint immobilization as simulations of microgravity, have shown decrease in cross-sectional areas of both major fiber types as well as areas of ultrastructural disorganization. Conversion of fibers from slow- to fast-twitch did not occur during bed rest. In the one-year Soviet bed-rest study contractile protein, metabolic, and energetic elements of the muscle fibers sustained significant losses. Exercise regimes ameliorated the atrophy and ultrastructural changes. During 30 days of bed rest, electrical stimulation of leg muscles was used to deter losses of muscle strength and fiber atrophy with some suggestions of success.

Animal studies, encompassing space flight and Earth-based simulations (suspension), have verified observations on human muscle and significantly extended our understanding of skeletal muscle changes in response to "microgravity." Investigations on muscles of animals, primarily the laboratory rat, have provided important insights into the histological, morphometric, functional, and biochemical changes of non-weight-bearing muscles as well as insights into the potential contributions of changes in extramuscular factors such as hormones, growth factors, and neural activity to the atrophic process. Space flight: Studies on rat skeletal muscle in the Soviet Cosmos space flights provided the first definitive evidence that muscle mass, strength, and fiber size were compromised, especially in the antigravity red muscle. These findings have been verified repeatedly in subsequent flights (Cosmos, Space Lab 3). Both fiber types atrophy, and a significant conversion of slow- to fast-twitch fibers occurs in as few as seven days. After two weeks of flight, the fast myosin isoform is increased. Degradative changes in muscle motor end plates and ultrastructure have been found along with foci of necrosis. Evidence of muscle regeneration has also been observed. The extensive loss of myofibrillar protein, greater than that of total muscle protein, suggests that contractile protein is preferentially lost. Muscle protein synthesis was decreased and catabolism appeared to be increased after flight. Muscle metabolism responds readily to microgravity as indicated by decreases or increases in the concentration and/or total quantity of numerous enzymes. Although in-vitro studies have demonstrated that muscle fibers require both tension and growth factors in order to hypertrophy, the precise role of endocrine and neural factors in space flight muscle atrophy is unknown. Furthermore, the mechanisms by which muscle tension causes hypertrophy are unknown. Microgravity Simulation Model: It is now clear that commonly used models (e.g. tenotomy, denervation, limb casting) for studying muscle atrophy on Earth do parallel

space flight atrophy of muscle. The development of the suspended rat model as a simulation has been the sine qua non for space-related laboratory studies. In virtually all regards, suspension, either head down or whole body, mimics faithfully muscle changes observed in space. The availability of this model has permitted investigations of mechanisms of atrophy, thereby providing a rational basis for the mechanisms of countermeasures. The use of the suspended rat further enables us to do many studies that may never be done in space and thus to focus on the most critical areas of study for the limited space flight opportunities. Losses of muscle mass in the suspended rat are almost identical to those observed in flight rats. Changes in fiber size, ultrastructure, and control of protein synthesis appear to be essentially identical in flight and suspension rats. Conversion of slow to fast fibers appears to be slower in the suspended rat. Countermeasures: The suspended rat has also been especially useful for the development of potential countermeasures of muscle atrophy. Treadmill running, standing, centrifugation, and ladder climbing are about equally effective, deterring the atrophy of the soleus muscle by about 50%. Ladder climbing appears to be the most effective in other muscles. A combination of ladder climbing and exogenous growth hormone have completely restored muscle mass in the suspended, hypophysectomized rat, proving to be the presently most effective countermeasure.

3.2 CRITICAL QUESTIONS (In priority order)

3.2.1 Organ Physiology

1. What is the time course and extent of muscle atrophy during either prolonged space flight or unloading?
2. Increase understanding of the regulation of muscle metabolism during normal activity and exercise, after acute and chronic unloaded states, and during recovery from unloading.
3. To what extent is muscle atrophy, structural change, and fiber type transformation reversible and recoverable?
4. What are the physiological similarities and differences of ground-based models of muscle atrophy and fiber transformation and weightlessness-induced muscle atrophy and fiber transformation? How valid are ground-based models for studying the characteristics of space-flight-induced muscle changes?
5. What are the morphological, biochemical and functional characteristics of space-flight-induced muscle changes?
6. What neuromuscular changes occur in space flight, and what role do these changes play in the changes in muscle structure and function?
7. What are the effects of weightlessness on the various systems (e.g. cardiovascular, nervous, endocrine) that influence the functional capacity of muscle, and how are these effects integrated?

8. What countermeasure programs are most effective for maintaining muscle structure and function? Determine efficacy of programs alternate to endurance type exercise. Are there alternative programs to endurance-type exercise that are effective?
9. Does the atrophy from unloading make muscle, tendon, and the myotendinous junction more susceptible to injury or damage on resuming normal weight-bearing states?
10. How completely and how well does injured muscle repair in microgravity?
11. What are the effects of embryonic and early extrauterine growth on the development of bone and muscle? Are there differences between weight-bearing and non-weight-bearing components of the system?

3.2.2 Cellular and Molecular

1. What are the molecular signals and mechanisms that are responsible for the control of muscle hypertrophy and atrophy, and what are the specific stimuli that are generated by exercise or disuse to signal increased or decreased protein accumulation in muscle cells?
2. What is the molecular interrelationship between catabolic and synthetic rates of protein metabolism in unloaded muscles?
3. What are the effects of altered levels of hormones and their receptors in regulating the physiology of unloaded muscle?
4. What is the link between mechanical activity (stress) and hormonal state in regulating protein turnover and gene expression and structure and function of muscle, as investigated by both ground-based and flight experiments? How can this information be used to integrate neuromuscular and musculoskeletal models of mechanics and adaptation to develop countermeasure protocols? How can experimental and theoretical musculoskeletal mechanics be used to measure and predict musculoskeletal forces and adaptation?
5. What is the role of specific hormones, pharmacologic agents, and growth factors in regulating protein and gene expression in response to unloading?
6. What additional knowledge is needed on the effects of unloading on the muscular intracellular and extracellular matrix?
7. What is the molecular basis for the effects of unloading on the susceptibility of muscle to injury or damage upon resuming normal weight-bearing states?

4.0 TECHNOLOGY

4.1 TECHNOLOGY FOR GROUND AND FLIGHT

1. In-vivo load and displacement sensing capabilities — Devices should be developed that will allow continuous monitoring of forces and position across muscle, bones, joints and other connective tissue. These devices should be usable in both man and experimental animal models.
2. Refinement of noninvasive technology to assess musculoskeletal mass — Smaller instrumentation requiring less power should be developed to monitor mass and volume changes of bone, muscle, and other connective tissue.
3. Development of hardware to measure bone and connective tissue integrity — Because mass and volume measurements alone do not indicate the functionality of bone and connective tissue strength, devices could be used both in simulated microgravity and true microgravity environments.
4. Cell culture systems for space flight — Gravitational biology is an important goal of scientific inquiry; using cell culture to determine changes in muscle, bone, and other connective tissues will allow in-depth investigation into cellular function and will help develop a molecular biological basis for future investigations.
5. Use of isotopes for assessing musculoskeletal metabolism — Both stable isotope and radioisotope labeling of the chemical components of intermediate metabolism should be developed to compare metabolism during ground-based microgravity simulation with that during actual flight experience.
6. Development of hardware for assessing macro- and microcirculation — Blood flow, changes in pH, nutrition, systemic hormones and local factors mitigate the changes seen in the musculoskeletal systems during microgravity living. Hardware to follow this change in animal models, both in simulated and in actual microgravity environments, should be developed.

4.2 TECHNOLOGY FOR FLIGHT ONLY

1. Flight qualifiable MRI and MRS — Magnetic resonance imaging and spectroscopy require significant weight and power and currently would be unacceptable for use on a space station; however, important volume and metabolic information can be obtained from such devices that are currently expanding our knowledge here on Earth.

2. Refinement of motion analysis systems for flight capabilities — In the near future time-motion, motion-force, muscle force-electrical activity, changes in joint loading, and bone impact vs. static forces must be determined to develop appropriate countermeasures for specific muscle groups and bone areas.
3. Development of non-invasive markers for assessing protein homeostasis — Protein constitutes a major component of the muscle and collagen that make-up the backbone and active components of movement in the musculoskeletal systems; it also is an important nutrient and regulator of systemic and local factors governing changes in organ turnover.
4. Flight qualifiable ultrasonics — This is a specific technology to assess mass that is important for quantifying changes in the musculoskeletal system during space flight for determining the natural history of organ loss and progress of countermeasures.
5. Flight capabilities for laboratory analyses — Both chemical and physical measurements are necessary to monitor physiologic changes occurring in crew members during space flight; it is vital to determine if the changes represent pathologic conditions.

5.0 RESEARCH STRATEGY

The musculoskeletal research area priorities for each of the NASA mission eras are presented in Tables 1a and 1b:

Table 1a

MUSCULOSKELETAL DISCIPLINE RANKINGS

MUSCLE	STS ERA CURRENT 1992-1995	SPACE STATION ERA 1991-2000	SPACE EXPLORATION ERA 2000-3000
EFFECTS OF LONG-DURATION SPACE FLIGHT			
MORPHOLOGY	9.5	7.5	6.5
BIOCHEMISTRY	9.5	10	10
FUNCTION	1.5	3	3
BIOMECHANICS	1.5	3	6.5
METABOLISM	4.5	7.5	8.5
COUNTERMEASURES	4.5	3	3
VALIDATION OF MODELS	7	7.5	3
NONINVASIVE MONITORING	9.5	3	3
MOLECULAR MECHANISMS	9.5	11	11
ROLE OF EXTRAMUSCULAR FACTORS (neural, endo., cv.)	4.5	7.5	8.5
REVERSIBILITY, RECOVERY AND REPAIR OF INJURY	4.5	3	3

Table 1b

MUSCULOSKELETAL DISCIPLINE RANKINGS

BONE, MINERAL, AND CONNECTIVE TISSUE	STS ERA CURRENT 1992-1995	SPACE STATION ERA 1991-2000	SPACE EXPLORATION ERA 2000-3000
ORGAN PHYSIOLOGY			
NATURAL HISTORY OF LOSS	5	4	8
ENDOCRINE & NUTRITION MECHANISMS	9	4	8
COUNTERMEASURES	2	4	3.5
HYPERCALCEMIA & STONE FORMATION	5	4	3.5
VERTIFICATION OF MODELS	5	4	3.5
REVERSIBILITY	9	4	3.5
HISTOLOGY & 3-D	9	10	10.5
PHYSICAL MECHANISMS (LOADING)	9	4	3.5
CELLULAR & MOLECULAR			
IN-VIVO FORCES	2	13.5	13.5
LOAD HISTORY MODELS	13.5	10	10.5
IDENTIFY MARKERS	2	8	8
ENDOCRINE RECEPTORS	13.5	13.5	13.5
GROUND MODELS	9	10	3.5
STRUCTURAL ASSEMBLY	13.5	13.5	13.5
MACROMOLECULE ASSEMBLY	13.5	13.5	13.5
SIGNAL TRANSDUCTION	16.5	16.5	16.5
TRANSLATIONAL CHANGE	16.5	16.5	16.5

Programmatic research opportunities could address the above critical questions in the following ways:

1. Human ground-based and flight experiments directed to the identification of physiologic, biochemical, biomechanical, or endocrine adaptation and to the development of appropriate physical or pharmaceutical countermeasures;
2. Animal ground-based and flight experiments (in rodents and squirrel and rhesus monkeys) to define the models and study basic and applied mechanisms of gravitational biology and therapeutics; and
3. Cell cultures to investigate cellular and molecular biology in bone, mineral, and connective tissues.

To accomplish the above objectives it will be necessary to integrate both basic and applied research across the experimental models chosen for study.

Research should draw upon the technology and knowledge base of the following science disciplines:

- Developmental and molecular biology
- Cellular physiology and biochemistry
- Systems physiology and biology.
- Biomechanics (orthopedic and neuromuscular)
- Biocomputation

As discussed in detail above, an underlying problem facing research on the musculoskeletal system in the context of microgravity is the well documented problem of muscle, connective tissue, and bone loss, which compromises not only the functional properties of this system, but the functional capability of man existing for long periods in a space environment. In addition, this problem of atrophy poses potential deleterious consequences for the recovery and readaptation of humans in Earth's environment. Consequently, in accomplishing the goal of this research program, a foundation will be laid toward determining, in particular, astronaut performance and readaptation as a consequence of the musculoskeletal system's response to exposure to microgravity environments for varying durations. Applied and basic research in microgravity will complement medical findings and treatments on Earthbound musculoskeletal diseases, especially in the areas of aging, osteoporosis, low back pain, arthritis, kidney stones, muscle wasting diseases, and cramps and postural instability.

To accomplish this research mission, experimentation must be undertaken using both human and animal research models involving both flight and ground-based experimental settings. In view of the limited access to research in a space

environment, the development of ground-based experimental models (both human and animal) focusing on the biological consequences of structural and functional unloading of the musculoskeletal system should be a high priority.

At the present time, three models for experimentation appear to be particularly suitable for addressing the specific objectives of the biomedical program. These include studies on humans, rodents, and nonhuman primates, the combination of which should enable the integration of both basic and applied research.

As described previously, the former two, in particular, have been instrumental in expanding our understanding of the effects of the microgravity environment on the integrity of the musculoskeletal system; whereas future research on nonhuman primates holds promise in bridging the gap between research on small animals and humans.

Life sciences research must identify possible consequences of weightlessness on the musculoskeletal system, understand the mechanisms of these effects, and develop effective and operationally practical countermeasures to protect crewmembers.

A confounding issue to the study of the response of human muscle in space travel is that there have not been any well controlled experiments conducted with humans in space. Most space-flight data have been collected without adequate controls. Without well controlled experiments in space, it will be impossible to determine the time course of muscle wasting during exposure to microgravity, what countermeasures may be effective, how they impact function during space flight, and how adverse effects of space travel can be overcome upon return to a 1-g environment. In spite of these limitations, attempts should be made to obtain as much information as possible concerning the effects of space-flight and other states of unloading on the muscle system.

Musculoskeletal research is the theme for Spacelab SLS-3 including rat, rhesus, and human subjects. Research on this flight will be important for validating the ground-based models of unloading as well as for developing a better understanding of the effects of space flight on the musculoskeletal system.

The following resource opportunities and requirements have been identified.

Flight

- Spacelab/Space Station Freedom for studying humans and animals for 16 to 180 days
- Capability for altering gravity from 0 to 2 g
- Sufficient space in laboratory facilities to allow for adequate human and animal physical activity
- Laboratory support capabilities for experimental perturbations (i.e. analysis and sampling)

- Unmanned flight capabilities to accommodate long-duration animal experiments
- Automation and telescience capabilities for life sciences experiments.

Ground-Based

- Characterization of human and animal (rodents and squirrel and rhesus monkeys) models for bone, muscle, and connective tissue studies
- Shared and integrated human and animal research opportunities in both university and NASA facilities
- Development of NASA Life Sciences Data Archival System (National Archival System).

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PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights ^a (1-14 days)	Long-Term Space Flights (more than 2 weeks) ^b	
		Pre- vs. Inflight	Pre- vs. Postflight
Cardiopulmonary System			
Heart rate (resting)	Slight increase inflight. Increased post-flight; peaks during launch and reentry, normal or slightly increased during mission. RPB ^c : up to one week.	Normal or slightly increased.	Increased. RPB ^c : 3 weeks.
Blood pressure (resting)	Normal; decreased postflight.	Diastolic blood pressure reduced.	Decreased mean arterial pressure.
Orthostatic tolerance	Decreased after flights longer than 5 hours. Exaggerated cardiovascular responses to tilt test, stand test, and LBNP postflight. RPB ^c : 3-14 days.	Highly exaggerated cardiovascular responses to inflight LBNP (especially during first 2 weeks), sometimes resulting in presyncope. Last inflight test comparable to R + O ^d (recovery day) test.	Exaggerated cardiovascular responses to LBNP. RPB ^c : up to 3 weeks.
Cardiac size	Normal or slightly decreased cardio/thoracic ratio (C/T) postflight.		C/T ratio decreased postflight.
Stroke volume	Increased the first 24 hours inflight, then decreased by 15%.	Same as short duration missions.	12% decrease on average.
Left end diastolic volume	Same as stroke volume.	Same as short duration missions.	16% decrease on average.
Cardiac output	Unchanged.	Unchanged.	Variable RPB ^c : 3-4 weeks.
Central venous pressure (indirect measurement)	Gradual decrease over 7 days inflight.	Not measured.	Not measured.
Left cardiac muscle mass thickness	Unchanged.	Unchanged.	11% decrease, return to normal after 3 weeks.
Cardiac electrical activity (ECG/VCG)	Moderate rightward shift in QRS and T postflight.	Increased PR interval, QT _c interval, and QRS vector magnitude.	Slight increase in QRS duration and magnitude; increase in PR interval duration.
Arrhythmias	Usually premature atrial and ventricular beats (PABs, PVBs). Isolated cases of nodal tachycardia, ectopic beats, and supraventricular bigeminy inflight.	PVBs and occasional PABs; sinus or nodal arrhythmia at release of LBNP inflight.	Occasional unifocal PABs and PVBs.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights* (1-14 days)	Long-Term Space Flights (more than 2 weeks) ^b	
		Pre- vs. Inflight	Pre- vs. Postflight
Systolic time intervals	Not measured.	Not measured.	Increase in resting and LBNP-stressed PEP/ET Ratio. RPB: 2 weeks.
Exercise capacity	No change or decreased postflight; increased HR for same O ₂ consumption; no change in efficiency. RPB: 3-8 days.	Submaximal exercise capacity unchanged.	Decreased postflight, recovery time inversely related to amount of inflight exercise, rather than mission duration.
Lung volume	Not measured.	Vital capacity decreased 10%.	No change.
Leg volume	Decreased up to 3% postflight. Inflight, leg volume decreases exponentially during first 24 hours, and plateaus within 3 to 5 days.	Same as short missions.	15% decrease in calf circumference.
Leg blood flow	Not measured.	Marked increase.	Normal or slightly increased.
Venous compliance in legs	Not measured.	Increased: continues to increase for 10 days or more; slow decrease later inflight.	Normal or slightly increased.
Body Fluids			
Total body water	3% decrease inflight.		Decreased postflight.
Plasma volume	Decreased postflight (except Gemini 7 and 8).		Markedly decreased postflight. RPB: 2 weeks increased at R + 0; decreased R + 2 (hydration effect).
Hematocrit	Slightly increased postflight.		
Hemoglobin	Normal or slightly increased postflight.	Increased first inflight sample; slowly declines later inflight.	Decreased postflight RPB: 1-2 months.
Red blood cell (RBC) mass	Decreased postflight; RPB: at least 2 weeks.	Decreased ~15% during first 2-3 weeks inflight; begins to recover after about 60 days; recovery of RBC mass is independent of the stay time in space.	Decreased postflight RPB: 2 weeks to 3 months following landing.
Red cell half-life (⁵¹ Cr)	No change.		No change.

Iron turnover			
Mean corpuscular volume (MCV)	Increased postflight; RPB: at least 2 weeks.		No change.
Mean corpuscular hemoglobin (MCH)	Increased postflight; RPB: 2 weeks.		Variable, but within normal limits.
Mean corpuscular hemoglobin concentration (MCHC)	Increased postflight; RPB: at least 2 weeks.		Variable, but within normal limits.
Reticulocytes	Decreased postflight; RPB: 1 week.		Variable, but within normal limits.
White blood cells	Increased postflight, especially neutrophils; lymphocytes decreased; RPB: 1-2 days. No significant changes in the T/B lymphocyte ratios.		Decreased postflight. In Skylab, RPB: 2-3 weeks for 28-day mission, 1 week for 59-day mission, and 1 day for 84-day mission.
Red blood cell morphology	No significant changes observed post-flight.	Increase in percentage of echinocytes; decrease in discocytes.	Increased, especially neutrophils; post-flight reduction in number of T-cells and reduced T-cell function as measured by PHA* responsiveness; RPB: 3-7 days; transient postflight elevation in B-cells; RPB: 3 days. Rapid reversal of inflight changes in distribution of red cell shapes; significantly increased potassium influx; RPB: 3 days.
Plasma proteins	Occasional postflight elevations in α 2-globulin, due to increases of haptoglobin, ceruloplasmin, and α 2-macroglobulin; elevated IgA and C ₃ factor.		No significant changes.
Red cell enzymes	No consistent postflight changes.	Decrease in phosphofructokinase; no evidence of lipid peroxidation and red blood cell damage.	No consistent postflight changes.
Serum/plasma electrolytes	Decreased K and Mg postflight.	Decreased Na, Cl, and osmolality; slight increase in K and PO ₄ .	Postflight decreases in Na, K, Cl, Mg; increase in PO ₄ and osmolality.
Serum/plasma hormones	Inflight increases in ADH, ANF, and decreases in ACTH, aldosterone and cortisol. Inflight decrease in glucose.	Increases in cortisol. Decreases in ACTH, insulin.	Postflight increases in angiotensin, aldosterone, thyroxine, TSH and GH; decrease in ACTH.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights ^a (1-14 days)		Long-Term Space Flights (more than 2 weeks) ^b	
	Pre- vs. Inflight		Pre- vs. Postflight	
Serum/plasma metabolites & enzymes	Postflight increases in blood urea nitrogen, creatinine, and glucose; decreases in lactic acid dehydrogenase, creatinine phosphokinase, albumin, triglycerides, cholesterol, and uric acid.		Postflight decrease in cholesterol, uric acid.	
	Decreased postflight.		Decreased postflight.	
Urine volume	Postflight increases in Ca, creatinine, PO ₄ , and osmolality. Decreases in Na, K, Cl, Mg.		Increased early inflight.	
	Decreases in Ca, creatinine, PO ₄ , and osmolality. Decreases in Na, K, Cl, Mg.		Increased osmolality, Na, K, Cl, Mg. Ca, PO ₄ . Decrease in uric acid excretion.	
Urine electrolytes	Decreased postflight.		Decreased early inflight.	
	Postflight increases in Ca, creatinine, PO ₄ , and osmolality. Decreases in Na, K, Cl, Mg.		Increased osmolality, Na, K, Cl, Mg. Ca, PO ₄ . Decrease in uric acid excretion.	
Urinary hormones	Decreased postflight.		Increased early inflight.	
	Postflight increases in Ca, creatinine, PO ₄ , and osmolality. Decreases in Na, K, Cl, Mg.		Increased osmolality, Na, K, Cl, Mg. Ca, PO ₄ . Decrease in uric acid excretion.	
Urinary amino acids	Postflight increases in 17-OH-corticosteroids, increase in aldosterone; postflight increases in cortisol, aldosterone, ADH, and pregnanediol; decreases in epinephrine, 17-OH-corticosteroids, androstosterone, and etiocholanolone.		Inflight increases in cortisol, aldosterone, and total 17-ketosteroids; decrease in ADH.	
	Postflight increases in taurine and β -alanine; decreases in glycine, alanine, and tyrosine.		Inflight increases in cortisol, aldosterone, and total 17-ketosteroids; decrease in ADH.	
Sensory Systems	Postflight increases in taurine and β -alanine; decreases in glycine, alanine, and tyrosine.		Increased inflight.	
	No change in thresholds postflight.		Increased postflight.	
Audition	Postflight increases in taurine and β -alanine; decreases in glycine, alanine, and tyrosine.		Increased inflight.	
	No change in thresholds postflight.		Increased postflight.	
Gustation & olfaction	Postflight increases in taurine and β -alanine; decreases in glycine, alanine, and tyrosine.		Increased inflight.	
	No change in thresholds postflight.		Increased postflight.	
Somatosensory	Postflight increases in taurine and β -alanine; decreases in glycine, alanine, and tyrosine.		Increased inflight.	
	No change in thresholds postflight.		Increased postflight.	

Vision	Transitory postflight decrease in intra-ocular tension; postflight decreases in visual field; constriction of blood vessels in retina observed postflight; dark adapted crews reported light flashes with eyes open or closed; possible postflight changes in color vision. Decrease in visual motor task performance and contrast discrimination. No change in inflight contrast discrimination, or distant and near visual acuity.	Light flashes reported by dark adapted subjects frequency related to latitude (highest in South Atlantic Anomaly, lowest over poles).	No significant changes except for transient decreases in intraocular pressures.
Vestibular system	40-50% of astronauts / cosmonauts exhibit inflight neurovestibular effects including immediate reflex motor responses (postural illusions, sensations of tumbling or rotation, nystagmus, dizziness, vertigo) and space motion sickness (pallor, cold sweating, nausea, vomiting). Motion sickness symptoms appear early in flight, and subside or disappear in 2-7 days. Postflight difficulties in postural equilibrium with eyes closed, or other vestibular disturbances.	Inflight vestibular disturbances are same as for shorter missions; markedly decreased susceptibility to provocative motion stimuli (cross-coupled angular acceleration) after 2-7 days adaptation period. Cosmonauts have reported occasional reappearance of illusions during long-duration missions.	Immunity to provocative motion continues for several days postflight. Marked postflight disturbances in postural equilibrium with eyes closed. Some cosmonauts exhibited additional vestibular disturbances post-flight, including dizziness, nausea, and vomiting.
Musculoskeletal system			
Height	Slight increase during first week inflight (~1.3 cm). RPB: 1 day.	Increased during first 2 weeks inflight (maximum 3-6 cm); stabilizes thereafter.	Height returns to normal on R + 0.
Mass	Postflight weight losses, average about 3.4%; about 2/3 of the loss is due to water loss, the remainder due to loss of lean body mass and fat.	Inflight weight losses average 3-4% during first 5 days; thereafter, weight gradually declines for the remainder of the mission. Early inflight losses are probably mainly due to loss of fluids; later losses are metabolic.	Rapid weight gain during first 5 days postflight, mainly due to replenishment of fluids. Slower weight gain from R + 5** to R + 2 or 3 weeks. Amount of postflight weight loss is inversely related to inflight caloric intake.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights* (1-14 days)	Long-Term Space Flights (more than 2 weeks)* Pre- vs. Inflight	Pre- vs. Postflight
Body composition		Fat is probably replacing muscle tissue. Muscle mass, depending on exercise regimens, is partially preserved.	
Total body volume		Center of mass shifts headward.	Decreased postflight.
Limb volume	Decreased postflight. Inflight leg volume decreases exponentially during first mission day; thereafter, rate of decrease declines until reaching a plateau within 3-5 days. Postflight decrements in leg volume up to 3%; rapid increase immediately postflight, followed by slower RPB. Decreased inflight and postflight; RPB: 1-2 weeks.	Early inflight period same as short missions. Leg volume may continue to decrease slightly throughout mission. Arm volume decreases slightly.	Rapid increase in leg volume immediately postflight, followed by slower RPB.
Muscle strength			Postflight decrease in leg muscle strength, particularly extensors. Increased use of inflight exercise appears to reduce postflight strength losses, regardless of mission duration. Arm strength is normal or slightly decreased postflight. Postflight EMGs from gastrocnemius show shift to higher frequencies, suggesting deterioration of muscle tissue; EMGs indicate increased susceptibility to fatigue. RPB: about 4 days.
EMG analysis	Postflight EMGs from gastrocnemius suggest increased susceptibility to fatigue and reduced muscular efficiency. EMGs from arm muscles show no change.		
Reflexes (Achilles tendon)	Reflex duration decreased postflight.		Reflex duration decreased postflight (by 30% or more). Reflex magnitude increased. Compensatory increase in reflex duration about 2 weeks postflight; RPB: about 1 month.

Nitrogen & phosphorus balance		Negative balances early in flight; less negative or slightly positive balances later in flight.	Rapid return to markedly positive balances postflight.
Bone density	Os calcis density decreased postflight. Radius and ulna show variable changes, depending upon method used to measure density.		Os calcis density decreased postflight; amount of loss is correlated with mission duration. Little or no loss from non-weightbearing bones. RPB is gradual; recovery time is about the same as mission duration.
Calcium balance	Increasing negative calcium balance in flight.	Excretion of Ca in urine increases during 1st month in flight, then plateaus. Fecal Ca excretion declines until day 10, then increases continually throughout flight. Ca balance is positive preflight, becoming increasingly negative throughout flight.	Urine Ca content drops below preflight baselines by day 10; fecal Ca content declines, but does not reach preflight baseline by day 20. Markedly negative Ca balance postflight, becoming much less negative by day 10. Ca balance still slightly negative on day 20. RPB: at least several weeks.

* Compiled from biomedical data collected during the following space programs: Mercury, Gemini, Apollo, ASTP, Vostok, Soyuz and Shuttle Spacelab.

* Compiled from biomedical data collected during Skylab and Salyut missions.

* RPB: Return to preflight baseline.